Methotrexate in the Treatment of Idiopathic Granulomatous Mastitis

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ABSTRACT. ***Objective.*** Idiopathic granulomatous mastitis (IGM) is a disfiguring inflammatory breast disease without effective treatment. We report the largest IGM cohort treated with methotrexate (MTX) monotherapy.

Methods. Chart review was performed on patients evaluated by the Stanford Immunology and Rheumatology Clinic, with histopathologically established IGM treated with MTX, and at least 1 followup appointment.

Results. Nineteen female patients with a mean age of 33.5 years were identified. Most failed treatment with antibiotics, prednisone, and surgical intervention. By 15 months of treatment with MTX, 94% had disease improvement and 75% achieved disease remission.

Conclusion. MTX monotherapy is an effective treatment for IGM. (First Release November 1 2019; J Rheumatol 2020;47:924–7; doi:10.3899/jrheum.181205)

Key Indexing Terms:
AUTOIMMUNE DISEASE GRANULOMATOUS MASTITIS METHOTREXATE

Idiopathic granulomatous mastitis (IGM) is a disfiguring inflammatory disease of the breast. It commonly presents as a unilateral, tender breast mass or localized induration with surrounding inflammatory changes and discomfort[1,2,3]. Compared to Western white populations (UK, USA, New Zealand), disease rates are higher among Middle Eastern (Egypt, Turkey, Iran) and Hispanic populations[1,4,5]. In 2006, a Pakistani study cited an incidence of 0.37%, while an American group reported a prevalence of 2.4 per 100,000 women[3]. These rates may not be accurate because owing to increasing incidence or awareness and diagnosis, there has been an abundance of cases of IGM reported in the literature in the past decade.

Patients initially present to primary care, gynecology, or the emergency room. Evaluation includes imaging with mammography, ultrasound, and magnetic resonance imaging with the intent of ruling out malignancy or other pathologies[2,3,6,7]. Diagnosis can be made with fine needle aspiration, core needle, incisional, or excisional biopsy. Typical histologic findings consist of non-caseating epithelioid and multinucleated giant cell granulomas centered on the mammary lobules. The cystic neutrophilic granulomatous mastitis (CNGM) pattern (or variant) has micro-abscesses and/or cystic vacuoles rimmed by neutrophils in the center[4,8]. The underlying cause of these findings remains elusive, although corynebacteria have been identified in CNGM. Autoimmune disease, infection and hormonal disruption have all been proposed as etiologies for IGM[5]. An autoimmune pathogenesis is favored given the inflammatory milieu of neutrophils, lymphocytes, and plasma cells and the treatment response to glucocorticoids and methotrexate (MTX)[4,5,7]. Other causes of granulomatous lesions must be excluded, including infections with mycobacteria, bacteria, or fungi, and systemic diseases such as granulomatosis with polyangiitis, sarcoidosis, and polyarteritis nodosa.

The optimal treatment for IGM remains unclear, but a lack of benefit from nontargeted antibiotic treatment has generally been accepted[1,9]. Until recently, most patients were treated with wide surgical excision or total mastectomy, with postsurgical recurrence rates as high as 50%[3,7]. High-dose glucocorticoids are often used, but have complications, including difficult wound healing and recurrence when stopped[7,10]. MTX has been used as a second-line treatment in patients with refractory disease, but has rarely been used as monotherapy. Available reports on the use of MTX have used low doses and have not evaluated monotherapy[2,7]. Nonetheless, complete remission rates with MTX treatment range between 70–80% and relapse rates are significantly lower compared to reports of surgical resections and prednisone use[2,7,9].

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Based on our initial experience using MTX as monotherapy for the treatment of IGM[11], patients have continued to be treated in this fashion at our institution. With further time and additional patient referrals, we now report on a larger cohort of patients treated with MTX as monotherapy for IGM.

MATERIALS AND METHODS

Institutional Review Board approval was obtained from Stanford University (protocol number 39416). The Stanford Translational Research Integrated Database Environment was queried to identify patients for inclusion in this study if they were evaluated by the Stanford Immunology and Rheumatology Clinic, had histopathologically established IGM, were treated with MTX, and had at least 1 followup appointment at the clinic. Additionally, patient demographics, medical history, IGM history, imaging, and duration and outcome of MTX treatment were collected. Improvement (positive change in symptoms from the prior visit) and/or remission (complete resolution while receiving therapy) of disease was defined by patient and provider assessment of clinical manifestations as documented in the medical record. Relapse was defined as worsening of disease on treatment or recurrence of disease after completion of treatment. Medication compliance was assessed by patient report and all patients were required to be using a contraceptive method (not including barrier methods) to receive MTX treatment.

RESULTS

Nineteen patients were identified who met the inclusion criteria (Table 1). All patients were female with a mean age of 33.5 years at the time of presentation. The majority were Hispanic (57.9%), followed by Asian (21.1%), African American (10.5%), and white (10.5%). The mean parity at presentation was 2 children with a latency between the last pregnancy and diagnosis of 30 months. Two patients (10.5%) were nulliparous. Ten patients (52.6%) reported prior use of hormonal contraception. Two patients (10.5%) had preexisting rheumatologic conditions including tenosynovitis and erythema nodosum. No patients reported a history of smoking tobacco. Seventeen patients (89.5%) had a negative Quantiferon-TB Gold blood test; 2 patients had a history of treated tuberculosis. Mean time from presentation to diagnosis was 6 months. Presenting symptoms were unilateral in 13 patients (68.4%) and included breast pain/tenderness (68.4%), mass/lump (52.6%), swelling (21.1%), erythema (26.3%), and induration (15.8%). Most patients had prior unsuccessful treatments with antibiotics (84.2%), incision and drainage (42.1%), prednisone (36.8%), MTX (10.5%), and surgical intervention (5.3%; Table 2).

Table 1. Main characteristics of 19 patients with granulomatous mastitis.

Characteristics	n (%)
Female sex	19 (100)
Mean age at presentation, yrs	33.5
Race	
Hispanic	11 (57.9)
White	2 (10.5)
African American	2 (10.5)
Asian	4 (21.1)
Mean age at menarche, yrs	11.8
Preexisting rheumatic disease	2 (10.5)
Prior use of hormonal contraception	10 (52.6)
Negative Quantiferon-TB Gold test	17 (89.5)
Mean parity at diagnosis	2
Mean time between last pregnancy and presentation, mos	30
Unilateral disease	13 (68.4)

MTX dosing was started at 10–15 mg/week and increased to 20–25 mg/week given per oral (PO) or subcutaneous (SC) routes based on clinical response. The mean MTX dose in the first 12 months of treatment was 18 mg PO weekly. SC MTX was used if the patient failed oral MTX prior to presentation to our clinic, had disease relapse under our management, or reported gastrointestinal side effects; otherwise, an oral preparation was used.

Within the first 3 months of treatment, 18 patients (94.7%) noted improvement of their disease with escalating doses of MTX as monotherapy. At 6 months, 94.4% had disease improvement and 22.2% were in remission. By 15 months of treatment, 94% had improved disease and 75% achieved disease remission (Figure 1). Median duration of treatment was 13–15 (range 1–30) months. At the time of manuscript submission, 12 of 19 patients demonstrated no evidence of disease and remained disease-free at followup on average (median) of 3 (range 1–7) years, 3 had ongoing treatment, 2 were lost to followup (1 moved away), and 1 failed to improve on treatment (Table 2). Three patients experienced side effects: 2 (10.5%) with nausea and 1 (5.2%) with elevated liver function tests (LFT). The former resolved with switching to SC administration, and the latter with a decreased treatment dose. The most common reason for termination of MTX treatment was disease remission.

A total of 3 patients (15.8%) had disease relapse while receiving MTX treatment. One patient relapsed between 7 and 9 months when MTX was held because of a lapse in contraception and elevated LFT. Continuation of MTX at a lower dose and subsequent increase resulted in disease remission. The other 2 patients relapsed between 10 and 12 months of treatment, but improved after changing to subcutaneous MTX. One additional patient had a disease recurrence while receiving no therapy during pregnancy. Only 1 patient (5.3%) failed to improve with MTX therapy and underwent mastectomy.

DISCUSSION

Six decades after its initial characterization, IGM continues to be a devastating, disfiguring disease, lacking standardized treatment. Surgical interventions continue to be practiced despite high recurrence rates. In both our practice and the literature, incision and drainage without adjuvant treatment is never curative; after wide surgical excision, recurrence occurs in up to half of patients[3,7]. The one patient in this study who underwent mastectomy experienced return of IGM within 1 year. While glucocorticoids are commonly initiated as the primary medical therapy for IGM, they have been used with limited success, unwanted side effects, and high rates of

Table 2. Disease history and treatment outcomes in 19 patients treated with methotrexate (MTX).

Patient	Time to Dx, mos	Presenting Symptoms	Prior Treatments	Average MTX Dose, mg	Treatment Duration, mos	MTX Treatment Outcomes
1	2	P, E, S, M	Abx	15	25–30	Remission at 7–9 mos; NED on 5-yr followup
2	5	P, S	None	9	22–24	Remission at 10–12 mos; NED on 2-yr followup
3	4	P	Abx I&D	15	25–30	Remission at 7–9 mos; NED on 5-yr followup
4	53	P, E, S	Abx, pred, I&D	13	4–6	Improvement; treatment ongoing
5	5	P, S, I	Abx, pred, I&D	21	19–21	Initial improvement on PO, relapsed at 10–12 mos; changed to SC with improvement at 13–15 mos; NED on 19–21 mos followup; treatment ongoing
6	1	I	Abx, pred	14	13–15	Remission at 7–9 mos; patient stopped therapy when wanted to conceive; NED on 2-yr followup
7	2	M	Pred, MTX	11	10–12	Remission at 4–6 mos; patient stopped treatment; NED 7 yrs
8	1	E, P	Abx, pred	11	16–18	Remission at 13–15 mo; patient stopped treatment; NED on 3-year followup
9	12	P, M	Abx, pred, MTX, exci, I&D	18	19–21	Previously on PO without improvement. Started on SC with remission at 7–9 mos and subsequent relapse when medication held for no birth control and elevated LFT. Restarted SC with remission again at 13–15 mos; NED on 3-yr followup
10	3	M	Abx	23	10–12	Remission at 10–12 mos; patient stopped treatment; NED 1-yr followup
11	3	P	Abx, I&D	20	10–12	No improvement on PO or SC therapy; underwent mastectomy
12	2	P, E, M	Abx	15	7–9	Remission at 4–6 mos; patient stopped treatment; NED 3-yr followup
13	1	M	None	15	22–24	Improvement; treatment ongoing
14	9	M	Abx	20	4–6	Improvement; lost to followup
15	3	M	Abx	13	4–6	Remission at 4–6 mos, patient stopped treatment; NED on 3-yr followup
16	1	P, M	Abx, I&D	20	1–3	Improvement at 1–3 mos; moved out of state
17	1	P, M	Abx	21	19–21	Remission at 4–6 mos; patient stopped treatment; NED 19-mo followup
18	3	P	Abx, pred, I&D	18	7–9	Improvement 7–9 mos; NED at 10–12 mos. Changed healthcare system – new lesion on left breast without treatment, not thought to be GM
19	2	P, E, I	Abx, I&D	21	16–18	Initial improvement then relapse at 10–12 mos, started on SC with improvement, changed to PO at 16–18 mos and remission by 24 mos; flare during pregnancy 1 yr later

Reason for treatment cessation is noted unless therapy was considered complete and stopped by treating physician. P: pain; E: erythema; S: swelling; M: mass; I: induration; Abx: antibiotics; pred: prednisone; I&D: incision and drainage; exci: excision; NED: no evidence of disease; LFT: liver function test; PO: per oral; SC: subcutaneous; GM: granulomatous mastitis.

recurrence[7,10]. In our previously reported cases of IGM treated successfully with MTX monotherapy, moderate doses of oral weekly MTX resulted in shrinking of the breast mass and accompanying symptoms over a period of months[11].

Of the 19 treated patients, 94% demonstrated notable improvement and 75% had disease resolution with the use of MTX as monotherapy. Only 15.8% of patients relapsed while on treatment but continued to improve/resolve when changed to SC administration. One patient relapsed during pregnancy, suggesting hormonal influences on disease. This cohort has comparable racial, age, and diagnostic findings to other published IGM cohorts[1,2,7,10].

In our 10 years of treating IGM with MTX, rapid and sustained responses occur with MTX doses between 15 and 25 mg PO or SC weekly for 12 months followed by gradual tapering over an additional 6–12 months, for a total of 18–24 months of treatment. Prior steroid treatment did not affect MTX efficacy. The average time from presentation to diagnosis did not change the treatment outcome, making a treatment effect with timing unlikely. Further, the use of MTX was associated with mild and easily reversible side effects. The limitations of our study include a small sample size and its retrospective features.

High recurrence rates after surgical interventions and increasing evidence for a local autoimmune disease pathogenesis have resulted in an increased volume of IGM referrals from gynecologists and breast surgeons to rheumatology colleagues[3,12]. While a few cases report treatment success with azathioprine or mycophenolate mofetil[7,13], prior studies[2,7,11] and our current cohort demonstrate a high level of efficacy of MTX. A commercially available, well tolerated, and easily monitored therapy, MTX is commonly used in rheumatology practice. Evidence of MTX utility in the treatment of IGM emphasizes the novel and integral role of the rheumatologist as a member of the multidisciplinary team required to care for patients with IGM.

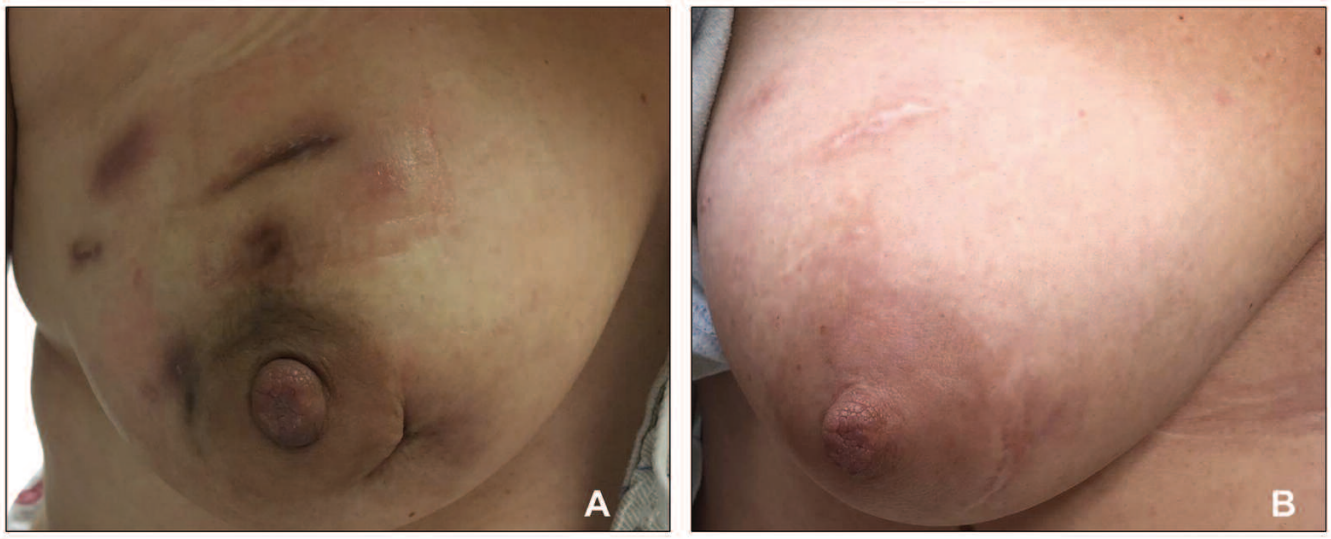

Figure 1. A 34-year-old woman with idiopathic granulomatous mastitis. A. After 4 months of treatment with antibiotics and prednisone, prior to treatment with methotrexate (MTX). B. After 18 months of treatment with MTX.

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